## NON-TECHNICAL ABSTRACT

We have demonstrated that the growth of HIV-1 can be blocked by the use of antisense genes. Specifically, we at Enzo designed three antisense genes that interfere with the functioning of two HIV-1 genes essential for virus growth in human cells. In experiments performed outside the body, we tested the effectiveness of these three antisense genes by introducing them into cultured human cells and then exposing these cells to HIV-1. We found that when the cells produced antisense RNA from these genes they were resistant to infection and destruction by HIV- 1. This resistance was a stable property of these cells, i.e. they were resistant to repeated exposures to HIV-1. The presence of these three genes had no apparent deleterious effect on the cells as indicated by tests that showed the presence of normal levels of cell proteins that characterize these cells as immune cells. When tested separately each of the three antisense genes was effective, but the three together were more effective than any one gene alone.

In an Enzo-sponsored clinical trial at the Medical School of the University of California at San Francisco our two Principal Investigators Morton J Cowan, M.D. and Marcus Conant, M.D. have put these three genes into blood stem cells. These cells serve as a reservoir of progenitor cells that divide and develop into CD4+ cells and other blood cells that can be infected by HIV-1. This trial tested whether these altered cells would serve as a long-term source for the replenishment of CD4 + and other blood cells. Drs. Cowan and Conant demonstrated that the anti- HIV-1 genes could be successfully put into the stem cells and that the stem cells themselves survived, grew and developed into CD4 + cells for at least as 6 months in all subjects (21 months in 2 subjects, to date) the end point of the experiment. The number of these cells that were successfully engrafted however was low.

In this present study, Dr. Amrita Krishnan working with Dr. John Zaia of the City of Hope Medical Center of Duarte, California and Dr. Marcus Conant, of the Medical School of the University of California at San Francisco plan to build upon these results by testing a procedure designed to increase the numbers of cells containing the anti HIV-1 antisense RNA gene. In this procedure they will remove and modify blood stem cells and then eliminate the stem cells left in the body (in the course of treating a form of cancer called Non Hodgkin's lymphoma) so that the modified cells will contribute a much larger percent of the final recovered blood cells. The goal of this study is to produce a continuous and renewable supply of CD4 + cells in large enough numbers to permit the determination of whether these cells will lower the viral load and will permit the reconstitution of the immune system.

In the proposed studies hematopoietic stem cells will be collected from the circulating blood of HIV-1-infected individuals. The anti HIV-1 RNA genes will be introduced into each subject's stem cells in the laboratory. The subjects will be treated for their cancer using chemotherapy and stem cell replacement. In the course of this treatment the engineered cells will be introduced back into these individuals. We will monitor these subjects to determine that this procedure is safe. We will also monitor the cells in each subject's blood for the presence of functioning anti HIV-1 RNA genes for a period of several months. Finally we will measure the level of HIV and the numbers of CD4+ cells in the blood. In this way we can determine the stability of the functioning anti HIV-1 genes within the body and the effect of the presence of these genes on the viral load and CD4 + cell count.